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09/665,472	09/20/2000	Menzo Havenga	4489US	8505

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TRASK BRITT
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EXAMINER

MARVICH, MARIA

ART UNIT	PAPER NUMBER
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1636

11

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/665,472

Applicant(s)

HAVENGA ET AL.

Examiner

Maria B Marvich, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 4, 7-8, 13-14, 16, 18, 19 and 21-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 4, 7, 8, 13, 14, 16, 18, 19 and 21-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6, 10.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

This office action is in response to an amendment filed 3/24/03, Paper Number 8. Claims 2-3, 5-6, 9-12, 15, 17 and 20 have been cancelled. Claims 1, 4, 7-8, 13-14, 16, 18, 19 and 21 have been amended. Claims 24 and 25 have been added. As no claim 23 is recited in the original claims or in the amended claims, claims 24-25 have been renumbered as claims 23-24 (Rule 1.126). Therefore, claims 1, 4, 7-8, 13-14, 16, 18-19, 21-24 are pending.

Response to Amendment

Receipt is acknowledged of an IDS submission on 3/24/03 (paper number 6) and 4/9/03 (paper number 10), which are compliant with 37 CFR 1.97 and 1.98. These submissions have been considered. The signed and initialed PTO 1449s have been mailed with this action.

Applicants' response indicates that drawings have been mailed separately to the Draftsperson. These substitute drawings have not been entered into the file. Upon receipt these drawings will be entered in to the file. Applicant will be notified in the next action if the replacement drawings are acceptable.

Receipt is acknowledged of an Oath/Declaration on 3/24/03 (Paper Number 9). The Declaration is proper and has been entered.

Receipt of a corrected abstract is acknowledged in which "means" is removed to place the abstract in proper form.

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Objections to claim 2 are withdrawn in light of cancellation of claim 2.

Rejection of claims 1-18 and 20-22 under 35 USC 112, first paragraph, have been withdrawn in light of cancellation of claims 2, 3, 5, 6, 9-12, 15, 17 and 20 and amendment to the remaining claims. Specifically, the claims have been amended to identify claimed subject matter as related to adenoviral vectors and capsids and not broadly on any viral vectors and capsids.

Rejection of claim 1 under 35 USC 112, second paragraph, is withdrawn in light of amendment to claim. Specifically, claim 1 has been amended to delete "having been provided with" and replacing it with "having".

Rejection of claims 2, 5, 6, 10-12 and 20 under 35 USC 112, second paragraph, has been withdrawn in light of cancellation of claims.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in 09/348,354 filed on 7/7/1999. No further claim to priority is noted.

Claim Objections

Claim 16 is objected to because of the following informalities: adenovirus is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 7-8, 13-14, 16, 18, 19 and 21-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Crystal et al. US 6,127,525. **This rejection is maintained for reasons of record in Paper No. 5, mailed 12/17/02. This rejection is hereby extended to newly added claims 23-24.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is unclear for reciting that the fiber protein is adenovirus 35. A fiber protein cannot be an adenovirus. It would be remedial to recite that the fiber protein is from adenovirus 35. **This is a new rejection necessitated by amendment.**

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Claim 22 recites the limitation "gene delivery vehicle" in claim 3. There is insufficient antecedent basis for this limitation in the claim. Claim 3 has been cancelled.

Claims 1, 4, 7, 8, 13, 14 and 16 are unclear in reciting that the vector has a first capsid and a second capsid. According to Life Science dictionary capsid is defined as

1. The protein covering, or outer coat, of a virus particle.

It is unclear how a vector can have two outer coats. **This is a new rejection necessitated by amendment**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and *In re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) State of the art. The invention recites a recombinant chimeric adenoviral vector with modified nucleic acid, which is modified such that an immune response is disabled in a host system.

While much effort has been directed at generating adenoviral vectors that can evade the immune system, success to date has been very limited. It is known that adenoviral activate innate immune response in host systems which is caused by the viral capsid (Liu and Muruve, Gene Therapy (2003) page 935, column 2. last paragraph). While advances have been made in reducing the immune response, the response has been disabled. Reduction of the response has been attempted by alteration of adenoviral nucleotides (Crystal et al. US 6,127,525 column 18, line 49-56) but more recently by inhibition of endosomal escape of the adenovirus (page 937, column 2, paragraph 2).

2) Unpredictability of the art. It is highly unpredictable that any modifications of the adenoviral nucleic acid would result in a adenoviral vector such that the immune response is disabled. The capsid proteins that are required for entry into the host cell elicit the host response. To date, no work has shown that this response can be disabled.

3) Number of working examples. Applicants disclose no working examples for how to modify the nucleic acid such that the immune response is disabled.

4) Amount of guidance provided by applicants. No guidance is provided for alterations that would need to be made in the nucleic acid of the adenovirus such that an immune response by a host system is disabled.

5) Nature of invention. This invention requires a combination of molecular cloning, viral and cell culture techniques.

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6) Level of skill in the art. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

7) Scope of the invention. This invention has a broad scope in that it recites a recombinant adenoviral vector with altered tropism to a dendritic cell.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification for how to reasonably determine how to modify the nucleic acid of the recombinant chimeric adenoviral vector such that the immune response is disabled.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue experimentation and excessive experimentation in order to practice the claimed invention

Response to Arguments

On pages 7-8 of the amendment filed 12/17/02, applicant traverses the rejection of claims 1, 4, 7-8, 13-14, 16, 18, 19 and 21-22 under 35 U.S.C 102(e) as anticipated by Crystal et al. Applicant argues that the claimed invention (vectors and capsids with fiber proteins of Ad 11,

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16, 35, 51 and 40L for tropism toward dendritic cells) is not anticipated, as Crystal et al do not disclose tissue tropism for dendritic cells. Instead Crystal discloses chimeric capsid proteins to reduce or eliminate recognition by neutralizing antibodies. Furthermore, applicant argues that Crystal et al "teach away" from the instant invention (page 8, line 1) as Crystal et al find that in switching specifically Ad7 fiber for that of Ad5, there is no escape from neutralizing antibodies against the Ad5 adenovirus. Applicant argues that Crystal et al do not teach capsids comprising the entire fibers from Ad11, Ad16 or Ad35 but at most Ad7 fiber proteins for the purpose of escaping neutralizing antibodies. Therefore, applicant states that Crystal et al. "can only be cited for the impermissible premise that it would have been obvious to try using the claimed fiber proteins to achieve a non-disclosed tropism". Finally, applicant argues, citing specifically the Ad7 fiber/Ad5 chimera of Crystal et al., that the inherency of this chimera for targeted tropism may not be established by probabilities or possibilities.

Applicant's arguments filed 3/24/03 have been fully considered but they are not persuasive. Crystal et al teach recombinant adenovirus in which capsid proteins such as the fiber protein can be generated in which the fiber protein is replaced in its entirety or in part with sequences of a fiber protein from a different serotype of adenovirus (column 11, line 55-58). Specifically disclosed serotype and adenovirus of the invention are serotype C (Ad5) and serotype F (Ad40) and serotype B (Ad11, Ad16, Ad35) (column 4, line 32-41). Therefore, Crystal et al teach capsids comprising the entire fibers from Ad11, Ad16 or Ad35.

The Ad7 fiber/Ad5 chimera of Crystal et al is merely used in the example as an embodiment of the chimera taught in the specification (e.g. Ad5 with the fibers from Ad11, Ad16, Ad35 and Ad40) and the teachings of Crystal et al are not intended to be limited to this

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specific chimera. Crystal et al teaches the means and the steps to generate the chimeric adenovirus vectors that are claimed in the instant invention. While the chimeric vector of Crystal et al is used for the avoidance of neutralizing antibodies, this does not exclude its use in altered tropism toward dendritic cells as it has tropism for dendritic cells inherent in its structure.

Applicants themselves have admitted that chimeric Ad5 adenovirus containing the fibers of Ad40, Ad11, Ad16, Ad35 will direct tropism towards dendritic cells. Applicants have not shown why one would expect that a chimeric adenovirus comprising the fiber of Ad11, Ad16, Ad35 Ad40l or Ad51 made according to the teachings of Crystal et al would not possess the ability to bind and infect dendritic cells. Absent evidence to the contrary, the vector and capsids made according to the teachings of Crystal et al, wherein one of the specifically recited fibers is inserted into a heterologous adenoviral capsid, would have at least some tropism for dendritic cells. As it is not clear based upon the teachings of record that the vectors of Crystal et al differ from those taught by the applicant such the vectors of Crystal et al cannot bind dendritic cells. In this case, inherency is not established by probabilities or possibilities but by the property of the chimeric adenovirus as taught by applicant's own specification.

That the Ad7 fiber switched for that of Ad5 does not escape from neutralizing antibodies, is not particularly relevant to the rejection because the claimed invention does not recite an Ad7 fiber/Ad5 chimera. The data do not "teach away" from the instant invention, as this data do not indicate that one could not make the claimed invention based upon Crystal et al. Absent evidence to the contrary, the failure of the Ad7 fiber/Ad5 chimera to escape neutralizing antibodies has no impact upon its ability to have altered tropism toward dendritic cells. Furthermore, whether a prior art reference "teaches away" is an important factor to weigh in

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dealing with obviousness and whether the data indicates that a combination of references would not have an expectation of success (see MPEP 2145 X.D). Instead, the teachings of Crystal et al fully anticipate the claimed adenovirus and the lack of escape from neutralizing antibodies does not teach one away from the ability to generate the chimeric adenovirus.

Claims 1, 4, 7-8, 13-14, 16, 18, 19 and 21-24 are rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3291.

Maria B Marvich, PhD
Examiner
Art Unit 1636

MM
June 2, 2003

DAVID GUZO
PRIMARY EXAMINER
